Attorney Docket No.: P-7562-US1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	SIEGEL, Steven	Examiner:	SHEIKH, Humera N.
Serial No.:	11/183,232	Group Art Unit:	1615
Filed:	July 18, 2005	Confirmation No.	8078
Title:	DRUG-CONTAINING IMPLANTS AND METHODS OF USE THEREOF		

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

I, Steven SIEGEL, a citizen of United States of America, residing at 740 Heatherstone Drive, Berwyn, PA 19312, hereby declare:

1. I am an Associate Professor at the University of Pennsylvania. I have more than fourteen years of experience in Biomedical Science and Neurobiology. I received my MD and PhD in Neurobiology at the Mount Sinai School of Medicine in 1996 after completing an undergraduate degree in Neuroscience at Colgate University in 1986. I later completed residency in Psychiatry and a Fellowship in Neuropsychiatry at the University of Pennsylvania before joining the faculty in 2001. I am currently the Director of the Translational Neuroscience Program in Department of Psychiatry and the Director of the Clinical Neurosciences Track for the School of Medicine at Penn. I am also a practicing psychiatrist specializing in the treatment of Schizophrenia.

2. My fields of research expertise include designing and developing surgically implantable long-term delivery systems for the treatment of schizophrenia

and other major neuropsychiatry conditions. My laboratory develops and validates animal models of schizophrenia and autism to foster better understanding of the disorders and their treatments.

3. I have read the above-identified patent application, of which I am a named inventor, and have reviewed its prosecution history, including the Office Action of October 27, 2010. The subject application describes, *inter alia,* a biodegradable implant comprising a therapeutic drug and a polymer.

4. Claims 1, 8, 14, 21-23, 29, 35, 36, and 97 are pending in this application. These claims are directed to a biodegradable implant comprising a therapeutic drug and a polymer, said polymer comprising polylactic acid (PLA) and polyglycolic acid (PGA) in a PLA:PGA molar ratio between 50:50 and 100:0, wherein said therapeutic drug is present in an amount of 10%-60% of the mass of said implant, and said polymer is present in an amount of 40%-90% of the mass of said implant, and wherein said therapeutic drug comprises risperidone, 9-OH-risperidone, or an active metabolite thereof.

5. The specification provides exemplifications of the claimed invention. Specifically, Example 7 shows risperidone loading concentrations of 10%-60%. It would be unreasonable to expect initial theoretical drug concentrations of 10% or more due to possible saturation and subsequent crystallization of the drug. Therefore, it was surprising that we could incorporate as much as 10-60% risperidone into the PLA:PGA copolymer, as claimed in the subject Application. Furthermore, in the subject Application, surprisingly and unexpectedly, the release of risperidone was achieved at the loading concentrations of 10%-60%. *See* Example 7 of the Specification.

6. In the Office Action dated October 27, 2010, the Examiner rejected claims 1, 8, 14, 29, 35, 36, and 97 under 35 U.S.C. § 103, as allegedly being obvious over U.S. Patent Application Publication 2002/0179096 ("Siegel") in view of U.S. Patent No. 5,871,778 ("Kino"). Specifically, the Examiner asserts that Siegel teaches a surgically implantable drug delivery device for long-term delivery of the antipsychotic drug – haloperidol. The Examiner acknowledges that Siegel

does not teach risperidone, but relies on Kino for this feature. Accordingly, the Examiner finds that it would have been obvious to combine the references to arrive at the invention.

7. I am the first-named inventor in the Siegel reference, discussed herein. The work described in the Siegel reference was conducted in my laboratory. I was the principal investigator for the work described in the Siegel reference.

8. Independent claim 1 recites "**therapeutic drug** is present in an amount of **10%-60% of the mass of said implant**, and said **polymer** is present in an amount **of 40%-90% of the mass of said implant**, and wherein said therapeutic drug is **risperidone**." [emphasis added]. Nowhere does Siegel teach or suggest this combination of claimed features. Rather, Siegel relates to haloperidol loaded implant, not risperidone loaded implant as claimed.

9. Kino does not cure the defect in Siegel. Specifically, Kino relates only to bromperidol or haloperidol loaded into dl-Polylactic acid or Poly(lactic-co-glycolic) acid (50:50) for making a microcapsule, which is not an implant as claimed. Although Kino describes a laundry list of active materials including risperidone, it provides no data or support for how much of each active ingredient that can be loaded in to each biodegradable polymer. Therefore, at the maximum, Kino provides a general guidance for producing only a microcapsule with no expectation of success with respect to specific amount of drug for each combination of the drug and the polymer for an implant.

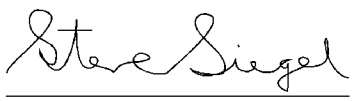
10. Examiner notes that "while the instantly claimed drug percentage/range is not explicitly taught, differences in concentration will not support patentability…unless…such concentration is critical." In response, I note that it is well known in the art that concentrations are, in fact, critical for making a polymer-based drug implant because of possible saturation and subsequent crystallization of the drug. Therefore, it would be unreasonable to expect initial theoretical drug concentrations of 10% or more, without any data.

11. In addition, a combination of a drug and a polymer may exhibit differing physio-chemical properties at various concentrations, and thus one could not expect or predict whether the arrangement and/or conformation of molecules in the crystal lattice would change while combining the drug and the polymer during solvent casting or other approaches to form an implant. Therefore, an attempt to incorporate as much as 10-60% risperidone into the PLA:PGA copolymer, as claimed in the subject Application cannot be expected in view of the Siegel reference, the Kino reference, or any other reference in the art. Accordingly, it would not have been obvious to modify Siegel's implant based on the Kino's laundry list of active materials.

12. Unexpectedly, as discussed above, risperidone loading concentrations of 10%-60% was achieved. *See* Example 7 of the Specification. As discussed above, it would be unreasonable to expect initial theoretical drug concentrations of 10% or more due to possible saturation and subsequent crystallization of the drug. Therefore, it was surprising that we could incorporate as much as 10-60% risperidone into the PLA:PGA copolymer, as claimed in the subject Application. Furthermore, surprisingly and unexpectedly, the release of risperidone was achieved at the loading concentrations of 10%-60%. *See* Example 7 of the Specification. These data clearly show the new, novel, and non-obvious biodegradable implant.

I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements, and the like so made, may jeopardize the validity of the application or any patent issuing thereon.

Date: 4/15/11



Dr. Steven Siegel